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Attempted rearrangement of N-nitrosolactams

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ATTEMPTED REARRANGEMENT OF N-NITROSOLACTAMS

by

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This Thesis

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I would like to express my appreciation to Dr. Howard E. Sheffer for his guidance and patience throughout the course of the project.

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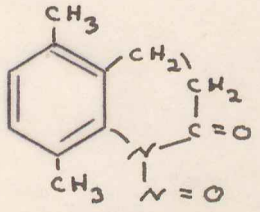
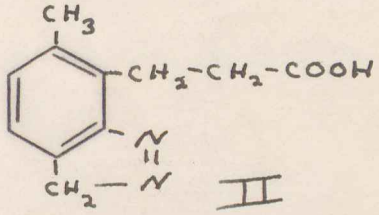
INTRODUCTION

This research was concerned with the preparation and subsequent attempted rearrangement of 5,8-dimethyl-N-nitrosohydrocarbostyril(I). The study was to show (1) whether rearrangement will occur to a cis- or trans- diazo



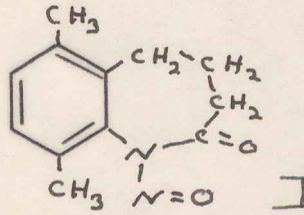
I



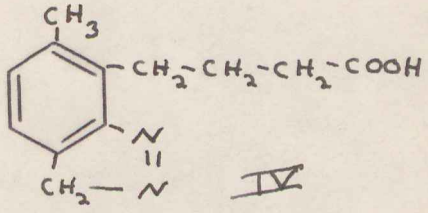
II

ester having an eight-membered ring, and (2) whether this ester is an intermediate in the formation of the 6-methyl-7-(β-carboxyacetyl)-indazole(II). The attempted rearrangements of I were performed in the presence and absence of β-naphthol.

Previous work in this area has been performed by H. Sheffer.[3] Sheffer, studying a homologue of I, has recently found that the product isolated from the rearrangement of 6,9-dimethyl-N-nitrosohomohydrocarbostyril(III) is 6-methyl-7-(γ-carboxypropyl)-indazole(IV).



III



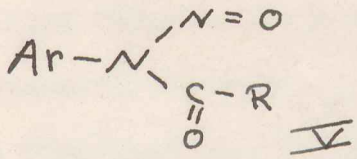
IV

This product probably results from the free-radical decomposition of a diazo ester, the initial rearrangement

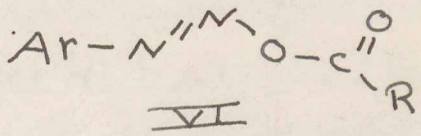
product of the N-nitrosolactam. This interpretation is consistent with R. Huisgen's results for the rearrangement of N-nitrosolactams.

HISTORICAL

In order to understand the very complex radical decompositions of diazo compounds, it is appropriate to begin by considering the nitrosoacylarylamines(V). The behavior of these substances is similar to that of the diazo compounds in that they react with aromatic hydrocarbons rather like alkaline diazo solutions with the formation of diaryls and they couple with phenols, though surprisingly in the ortho position. From this analysis it was not far-fetched to think of tautomerism with diazoacylates(VI).



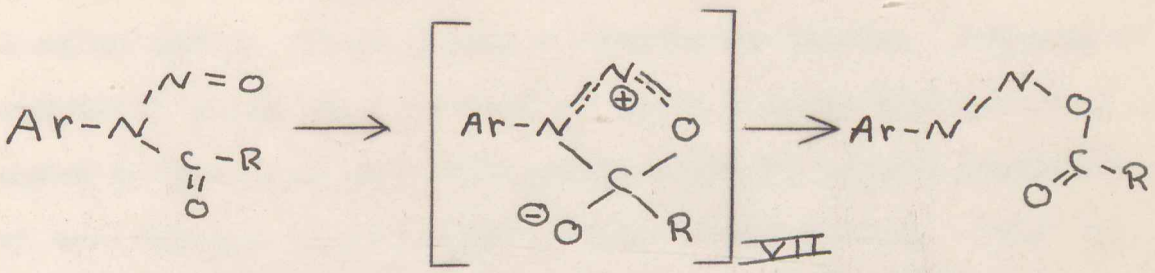
V



VI

In the early 1950's DeTar and Huisgen concerned themselves with the conversion of nitrosoacylarylamine into the diazoacylate and they maintained that the homolysis is a rapid reaction following the rate-determining rearrangement of the nitrosoacylarylamine into the metastable diazoacetate. This is the "rolling off" mechanism put forth by Huisgen. The rearrangement proceeds in an inert media. A favorable effect from polar solvent is hardly perceptible and therefore a mechanism involving the separation of free acyl cation is not likely. Huisgen postulated that the appearance of free ions could be avoided by a simultaneous exchange of acyl residues between two molecules of the nitroso compound, but,

since the acyl migration rigidly adheres to the first order, it must consist of an intra- and uni-molecular isomerization. Huisgen and Krause[1] describe the rearrangement as a rolling off through a state(VII) in which a four-membered ring stabilized by mesomerism is present.



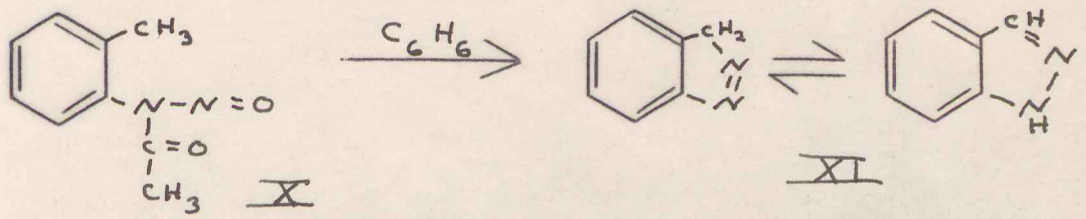
According to the latter description, acyl migration should result in the trans-diazotate. Huisgen[2] was able to confirm this by studying the conversion of N-nitrosobenzolactams(VIII) into cyclic diazo esters(IX). The fact that the five-membered ring compound(VIII,n=1) did not rearrange, whereas the corresponding homologues with seven- and eight-membered rings(n=3or4) did so smoothly implies that the trans- and not the cis- form must be present in the products. Huisgen was unable to prepare the nitroso compound(VIII,n=2) and therefore no information exists as to whether this compound would undergo the proposed rearrangement.

This investigation of the homologus series of N-nitrosolactams and their capability for acyl migration settled the question of whether the resulting diazo ester contains the diazo system in cis or trans configuration. With a cis-diazo ester, the system would already be free from strain with the rearrangement of the five-membered N-nitrosolactam(VIII,n=1) to the expected 7-membered ring diazo ester with cis configuration of the nitrogen to nitrogen double bond. However this

rearrangement was not observed. While the cis- olefinic grouping can be fit into a real small ring, it is necessary to have a series of elements in order to bridge the trans-positions of a double bond system. The smallest known trans-cyclo olefin is the trans-cyclooctene, which according to K. Ziegler and H. Wilms exerts a remarkable strain. Huisgen's model(IX) shows that we need at least a nine-membered ring in order to build an only moderately strained cyclic diazo ester of the formula IX(n=3) with a trans-diazo system. Only for the ten-membered ring(n=4) is the model free of strain. Huisgen's experimental results confirm this theory.

H. Sheffer[3], interested in the Jacobson reaction, began an investigation to determine whether this reaction proceeds through the mechanism propounded by Huisgen. In this reaction N-nitroso-N-aceto-o-toluidide(X) placed in an inert media (benzene) rearranges to indazole(XI).

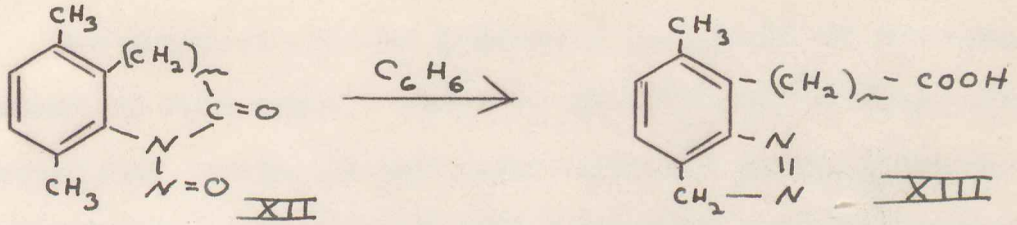
Jacobson Reaction



X XI

In Sheffer's reaction 6,9-dimethyl-N-nitrosohomohydrocarbostyril(XII,n=3) rearranges under similar conditions to 6-methyl-7-(γ-carboxypropyl)-indazole(XIII) presumably through the trans-diazo ester postulated by Huisgen.

Sheffer Reaction



XII XIII

A study of XII(n=2) would help to fill in the gap in Huisgen's investigations and to expand our study as to whether the Jacobson rearrangement proceeds via the metastable, cyclic trans-diazo ester.

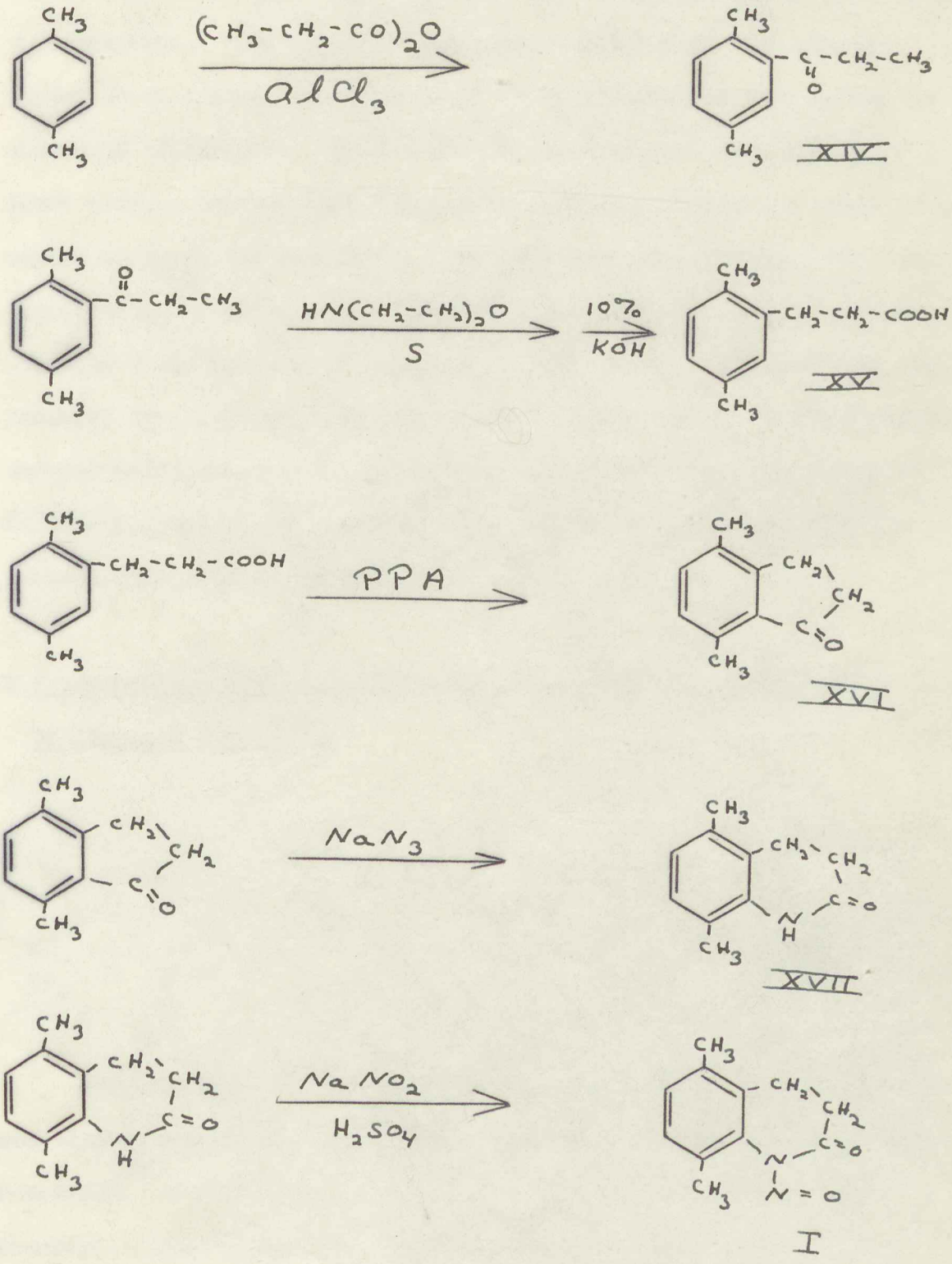
APPARATUS

The majority of the apparatus consisted of the usual laboratory equipment. However, in addition to this, more specialized apparatus was later employed among which the Perkin-Elmer Model-21 infrared recording spectrophotometer, Varian Model A-60 nuclear magnetic resonance spectrometer, and the Perkin-Elmer Model-202 ultraviolet-visible recording spectrophotometer were notable examples. The Perkin-Elmer Model-21 infrared recording spectrometer was equiped with NaCl optics. Materials could be run pure or dissolved in a solvent with little or no absorbance such as chloroform.

The infrared spectrophotometer and the nuclear magnetic resonance spectrometer were useful in determining the functional groups present in the various reaction products and also for the elucidation of the structure of some of these compounds. The ultraviolet-visible spectrophotometer was used to study the coupling reaction between the N-nitroso compound and β-naphthol.

EXPERIMENTAL

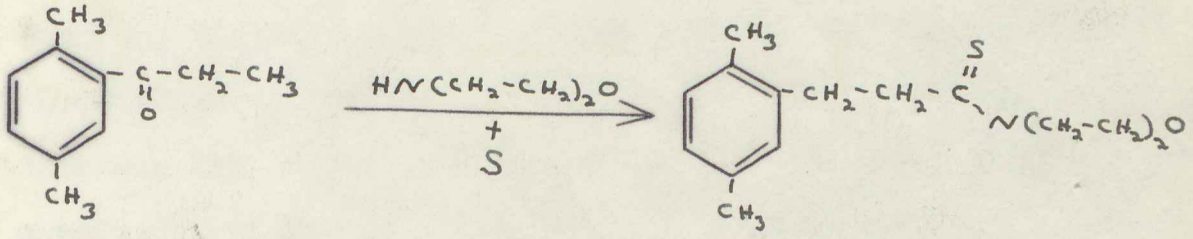
Proposed Reaction Sequence for the Preparation of 5,8-Dimethyl-N-Nitrosohydrocarbostyril



1. Preparation of 2,5-Dimethylpropiophenone

The 2,5-dimethylpropiophenone(XIV) was prepared from p-xylene and propionic anhydride by the method described by Adams and Johnson.[4] The reaction was carried out at ice bath temperature. One mole of propionic anhydride was slowly added to a mixture of one mole of p-xylene and 2.4 moles of aluminum chloride. This mixture was stirred for one-half hour with a mechanical stirrer and then allowed to stand overnight at room temperature. The mixture was poured into concentrated hydrochloric acid(600ml.) and 600 grams of crushed ice and then extracted with ether(150 ml.). The solvent was removed by distillation from a steam bath and the remaining ketone was obtained by fractional distillation. A yield of 66%(107g.) of 2,5-dimethylpropiophenone boiling at 239-241°C (corrected) was obtained.

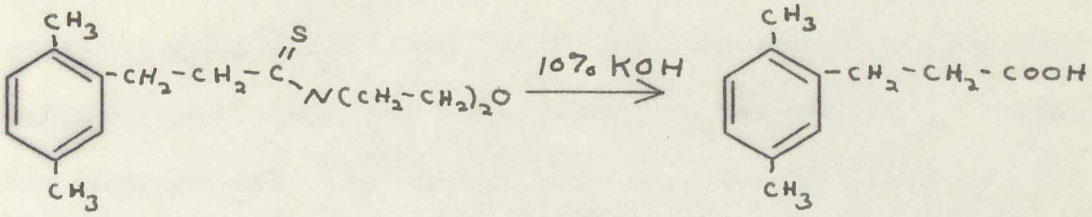
2. Preparation of β-2,5-Dimethylphenylpropiothiomorpholide-Willgerodt Reaction



Preparation of β-2,5-dimethylphenylpropiothiomorpholide was attempted by the Kindler modification of the Willgerodt reaction.[5] A mixture of 0.10 moles of 2,5-dimethylpropiophenone, 0.10 moles of morpholine, and 0.10 moles of sulfur

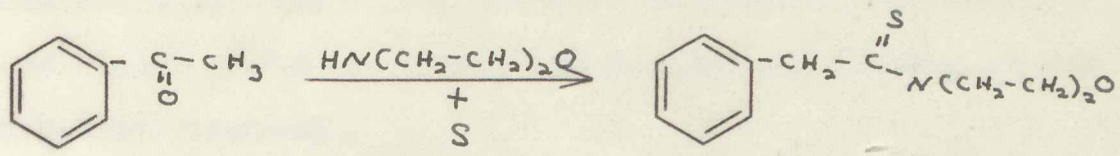
was refluxed for eight hours. The reaction mixture was diluted with 125 ml. of water and extracted with ether. The dried ether layer was evaporated and an oily residue remained. Crystallization of the product was attempted from an ethanol-water solvent system but no product separation was effected.

3. Hydrolysis of β-2,5-Dimethylphenylpropiothiomorpholide



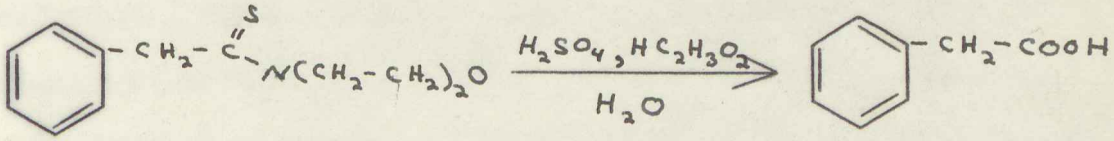
An attempt was made to hydrolyze the crude thiomorpholide product to the β-(2,5-dimethylphenyl)-propionic acic(XV).(6) A mixture of 1.65 grams of the crude thiomorpholide product and 25 ml. of 10% KOH were refluxed for 19 hours. Ether was then added to the cooled reaction in order to remove the unreacted organic products. The aqueous layer was acidified and greyish crystals (0.50g.) separated which did not melt or burn but rather formed a charred product when placed into a direct flame. Sodium fusion test was run on the crystals for nitrogen and sulfur. Both tests were negative indicating the absence of either of these elements in the sample.

4. Preparation of Phenylacetothiomorpholide



Since β-(2,5-dimethyl)-phenylpropiothiomorpholide could not be isolated, the preparation of phenylacetothiomorpholide was carried out in an attempt to investigate the technique involved with the Willgerodt reaction. Acetophenone(0.20 moles), morpholine(0.2 moles), and sulfur(0.2 moles) were refluxed for nine hours according to the method of Campaigne.(16) The mixture was poured into hot 95% ethanol and a yield of 46%(44g.) of thiomorpholide product melting at 76-78°C was obtained.

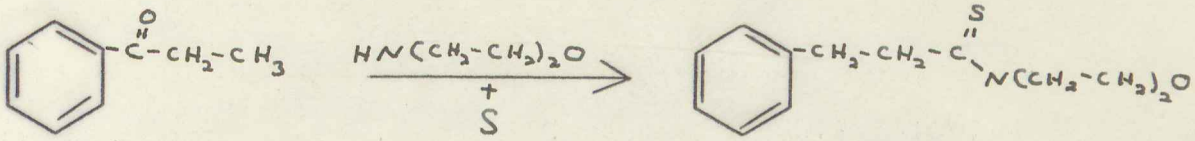
5. Hydrolysis of Phenylacetothiomorpholide



The hydrolysis of phenylacetothiomorpholide to phenylacetic acid was performed by the method of Campaigne.(16) The mixture of thiomorpholide(0.05 moles), sulfuric acid(7.4g), acetic acid(29.0g.), and water (6.0g.) was refluxed for five hours. The reaction mixture was poured into 200 ml. of water and a crude product(orange crystals) was separated out. These crystals were heated with 5% sodium hydroxide(50 ml.) for a

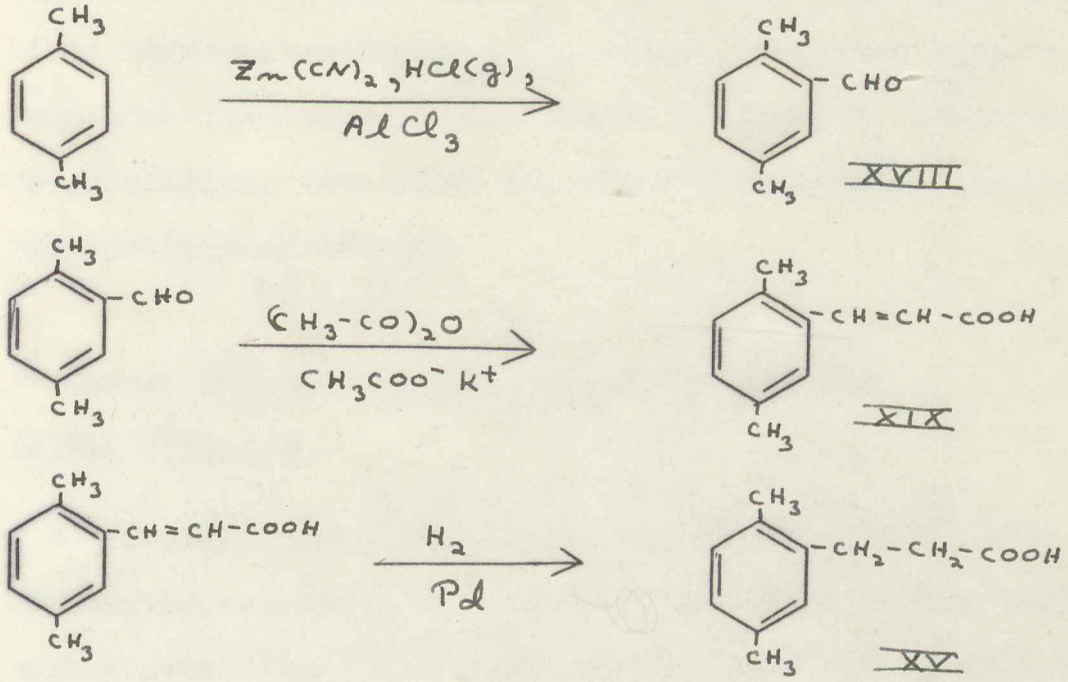
few minutes. The hot solution was filtered from the insoluble matter and acidified with 6N hydrochloric acid. A 9%(0.6g.) yield of acid(colorless plates) melting at 74-76°C were obtained.

6. Preparation of β-Phenylpropiothiomorpholide



The preparation of β-phenylpropiothiomorpholide was carried out under the general reaction conditions specified for the Willgerodt Reaction.(5) Propiophenone(0.2 moles), morpholine(0.2 moles), and sulfur(0.2 moles) were refluxed for eight hours. The reaction mixture was poured into 100 ml. of hot 95% ethanol but no crystallization could be effected. Some of the ethanol was evaporated and to the resulting solution was added 200 ml. of water. This was extracted with ether. The ether layer layer was dried with anhydrous sodium sulfate and the ether evaporated. A small yield of light brown crystals were obtained which melted at 133-136°C. The weight of the yield was not measured because of the small amount of crystals obtained. From these results it became evident that the Willgerodt reaction would not be a feasible method of producing the desired β-(2,5-dimethylphenyl) propionic acid.

Alternate Reaction Sequence for the Preparation of β-(2,5-Dimethylphenyl)-Propionic Acid



7. Preparation of 2,5-Dimethylbenzaldehyde-Gatterman Synthesis

The Gatterman synthesis was used to prepare 2,5-dimethylbenzaldehyde(XVIII).(7) Two moles of p-xylene, one mole of zinc cyanide and 2.93moles of aluminum chloride were mixed at ice bath temperature. The reaction was then heated and at 60°C the passage of HCl gas was started. Using a glycerol bath the temperature was maintained at 90°C for five hours but the passage of HCl gas was discontinued after two hours. After

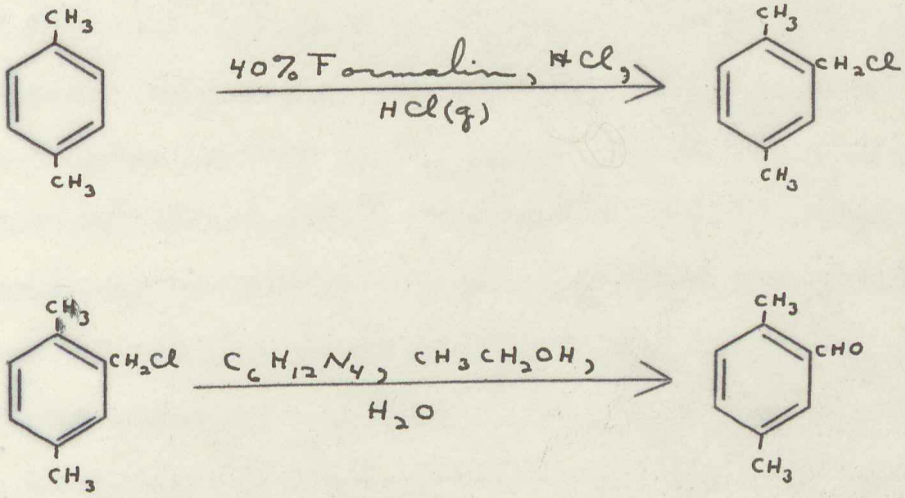
standing overnight the viscous reaction product was poured onto a mixture of 500 grams of ice and 50 ml. concentrated hydrochloric acid and distilled in steam. The crude aldehyde thus obtained was taken up in ether, the ether layer dried, and pure 2,5-dimethylbenzaldehyde obtained by fractional distillation. The yield was 84% aldehyde(109g.) boiling at 217-219°C(uncorrected).

8. Preparation of β-2,5-Dimethylcinnamic Acid-Perkin Reaction

Freshly fused potassium acetate(0.14 moles), 2,5-dimethylbenzaldehyde(0.14 moles), and acetic anhydride(0.29 moles) were mixed in a round bottom flask with an air cooled reflux condenser 60 cm. in length. The reaction was carried out for four and one-half hours at 160-170°C. The hot reaction mixture was poured into 800 ml. of boiling water and steam distilled to remove the unreacted aldehyde. The residual liquid was cooled, 3.0 grams of norite added, the mixture boiled gently for ten minutes, and then quickly filtered. The filtrate was acidified and crystals of β-2,5-dimethylcinnamic acid(XIX) were collected in 9% yield(2.1g.). A melting point taken on the crystals gave the following results: m.p. 123-126°C, 136-139°C, and 158°C. From these values it became evident that the ring methyl groups had undergone migration under the influence of aluminum chloride during the Gattermen synthesis and the aldehyde formed was

a mixture of 2,5-, 2,4-, and 3,5-dimethylbenzaldehyde. Niedzielski and Nord[8], studying the Gatterman reaction in sodium cyanide, stated that although p-xylene has a zero dipole moment it can undergo migration and alkylation by the aluminum chloride to form the more highly polar hydrocarbon.

Alternate Reaction Sequence for the Preparation of 2,5-Dimethylbenzaldehyde



9. Preparation of 2,5-Dimethylbenzyl Chloride

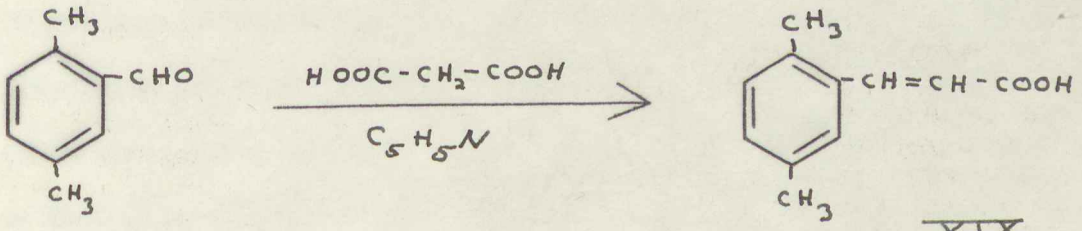
The chloromethylation of p-xylene was carried out as described by Adams[9]. One mole of p-xylene was mixed with an equal weight of 40% formalin(1.3 moles of formaldehyde) and five times its weight of concentrated hydrochloric acid. The mixture was stirred mechanically at 60-70°C for seven hours during which time a stream of HCl gas was introduced. The

reaction product mixture consisted of two separate layers and the resulting oil(top layer) was taken up in 200 ml. of ether. Vacuum distillation gave a yield of 51% 2,5-dimethylbenzyl chloride(XX)(78g.) boiling at 102.5-105.5°C at 20 mm.

10. Preparation of 2,5-Dimethylbenzaldehyde-Sommelet Reaction

2,5-Dimethylbenzaldehyde was prepared from 2,5-dimethylbenzyl chloride by the Sommelet reaction.(10) To a mixture of 0.85 moles of 2,5-dimethylbenzyl chloride and 500 ml. of ethanol were added, with shaking, 0.68 moles of hexamethylenetetramine and 100 ml. of water. After five minutes the additional water(400 ml.) was added and the mixture was heated under reflux for two hours. The product was steam distilled and the resulting compound was taken up in ether. Vacuum distillation of the dried ether layer gave a yield of 61% 2,5-dimethylbenzaldehyde(70g.) boiling at 104-105.5°C at 18mm.

11. Preparation of 2,5-Dimethylcinnamic Acid-Doebner Reaction



XIX

The 2,5-dimethylcinnamic acid(XIX) was prepared by this method instead of the previously described Perkin reaction.(11) The mixture of 2,5-dimethylbenzaldehyde(0.54 moles), malonic acid(0.54 moles), and pyridine(0.16 moles) was heated at 100°C until all the carbon dioxide was evolved(5½ hours). This mixture was poured into 600 ml. of water and 25 ml. concentrated hydrochloric acid and was steam distilled to remove the unreacted aldehyde. The acid was crystalized by adding 12 ml. concentrated hydrochloric acid to the hot solution which was then cooled. A yield of 70%(7.4g.) of acid was obtained melting at 129-131°C.

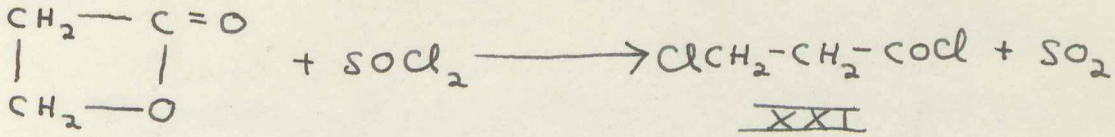
12. Preparation of β-(2,5-Dimethylphenyl)-Propionic Acid

β-(2,5-Dimethylphenyl)-propionic acid(XV) was prepared by the hydrogenation of 2,5-dimethylcinnamic acid. The unsaturated acid(0.2 moles) was dissolved in ethanol. Then 0.1 grams of palladium on powdered charcoal was added, and the mixture was shaken under pressure of hydrogen gas for five hours. The reaction mixture was filtered to remove the palladium catalyst. The ethanol solvent was evaporated on a rotary evaporator, the residue was taken up in 5% sodium bicarbonate solution, extracted with petroleum ether, and then the aqueous layer was acidified with concentrated hydrochloric acid. A yield of 96%(34g.) of acid was obtained with a melting point of 42-43°C.

13. Preparation of 4,7-Dimethylindanone-1

4,7-Dimethylindanone-1(XVI) was prepared by the cyclodehydration of β-(2,5-dimethylphenyl)-propionic acid.[12] Polyphosphoric acid(254g.) was heated to 70°C at which time the acid(0.14 moles) was added. The mixture was heated between 65-70°C for one hour and 20 minutes with constant stirring. At this time there appeared an intense red color which signified that the reaction had been completed. The hot mixture was poured into 500 grams of ice water to decompose the red complex and to effect the crystallization of the indanone product. A yield of 75%(16g.) of 4,7-dimethylindanone-1 was obtained which melted at 74-76°C. The product was recrystallized from methanol.

14. Preparation of β-Chloropropionyl Chloride



$$\begin{array}{l} CH_2 - C=O \\ | \quad\quad | \\ CH_2 - O \end{array} + SOCl_2 \longrightarrow \underset{\text{XXI}}{ClCH_2-CH_2-COCl} + SO_2$$

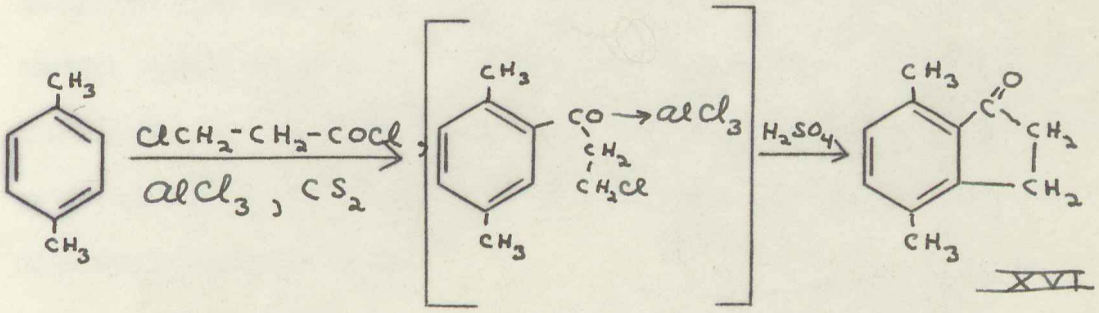
β-Chloropropionyl chloride was prepared from β-propiolactone by the method of Gresham and Shaver.[13] To 1.2 moles of thionyl chloride, there was added 1.0 mole of β-propiolactone over a period of three hours with constant stirring of the solution. The reaction is extremely exothermic and the β-chloropropionyl chloride(XXI) was retained in the reaction flask by use of a water cooled condenser. Vacuum

distillation of the product gave yields ranging from 20-40% boiling at 80-86°C at 100 mm. Large amounts of unreacted thionyl chloride were recovered after each reaction thus indicating the incomplete nature of the reaction. However no quatitative measures of the unreacted compounds were recorded.

15. Preparation of 4,7-Dimethylindanone-1

Alternate Method

Another method to synthesize 4,7-dimethylindanone-1(XVI) from β-chloropropionyl chloride was described by Hart and Tebbe.[14]



This method involves the simultaneous acylation and alkylation of an aromatic nucleus by a β-halo acid chloride. A solution of 0.21 moles of β-chloropropionyl chloride and 0.20 moles of p-xylene in 25 ml. of carbon disulfide was added over 45 minutes to aluminum chloride(0.24 moles) covered with 125 ml. of carbon disulfide. After three hours of stirring at room temperature, the carbon disulfide was removed at an aspirator and to the residual dark oily complex was added concentrated sulfuric acid(250 ml.). The acid is

used to break the carbonyl-aluminum chloride complex and also to effect alkylation of the aromatic nucleus. After heating this mixture at 90°C for 45 minutes, it was poured onto 1 kg. of crushed ice. The product was extracted with ether and benzene and these solvents were replaced by methanol. A yield of 63% of indanone product(20g.) melting at 76-77.5°C was obtained. A mixed melting point was taken of this compound and the 4,7-dimethylindanone-1 synthesized by the previous method and this melted at 75.5-77 C thus showing no melting point depression. Infrared spectra were run of both compounds in chloroform and these spectra proved to be identical. Running the reaction in the presence of aluminum chloride at room temperature had no tendency to cause migration of the methyl groups attached to the aromatic nucleus. As previously shown a different effect was observed with aluminum chloride at 90°C in the preparation of 2,5-dimethylbenzaldehyde.

16. Preparation of 5,8-Dimethylhydrocarbostyril-Schmidt Reaction

The preparation of 5,8-dimethylhydrocarbostyril(XVII) from 4,7-dimethylindanone-1 was carried out under conditions similar to those described by Sheffer.(3) To the solvent, methane sulfonic acid, there was added 0.14 moles of 4,7-dimethylindanone-1 and this mixture was then placed in an ice water bath. While keeping the reaction cool(5-15°C),

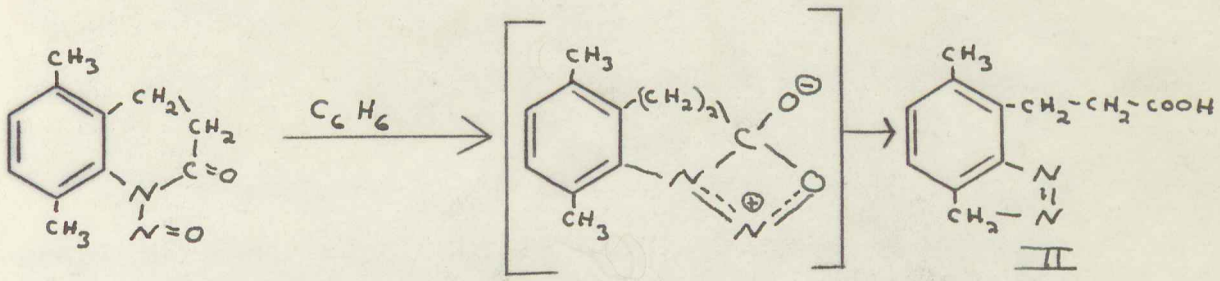
sodium azide(0.195 moles) was added in small portions over a half hour period. After the addition of the sodium azide was completed, the reaction was allowed to proceed at room temperature with constant stirring for two and one-half hours. The reaction mixture was poured into ice water and a yield of 63%(16g.) of 5,8-dimethylhydrocarbostyril melting at 125-128°C was obtained. A recrystallization of the product was made using a water-ethanol solvent system.

17. Preparation of 5,8-Dimethyl-N-Nitrosohydrocarbostyril

The preparation of 5,8-dimethyl-N-nitrosohydrocarbostyril(I) from 5,8-dimethylhydrocarbostyril was carried out by the method of Sheffer.(3) The gas generator for the production of nitrous acid(HONO) consisted of dropping concentrated sulfuric acid onto sodium nitrite. The gas produced was bubbled through a fritted-glass tube into the reaction mixture which consisted of 5,8-dimethylhydrocarbostyril(0.05 moles) in acetic anhydride(28 ml.), acetic acid(84 ml.), and pyridine(4.0 ml.). The reaction was continued for 15-20 minutes during which time the slightly yellow solution turned to a dark green color. During the entire procedure, the reaction mixture was immersed in an ice water bath at 0-5°C. This mixture was now poured onto ice(350g.). Recrystallization from a water-methanol solvent system gave a yield of 82%(8.0g.) of the N-nitroso compound melting at 81-82°C.

18. Attempted Rearrangement of 5,8-Dimethyl-N-Nitrosohydrocarbostyril

The rearrangement of 5,8-dimethyl-N-nitrosohydrocarbostyril was attempted according to the method of Sheffer.(3) The N-nitroso compound was put into 125 ml. of benzene which had been previously dried over sodium and the mixture was allowed to stand at room temperature overnight. The desired rearrangement should consist of the following sequence of steps.

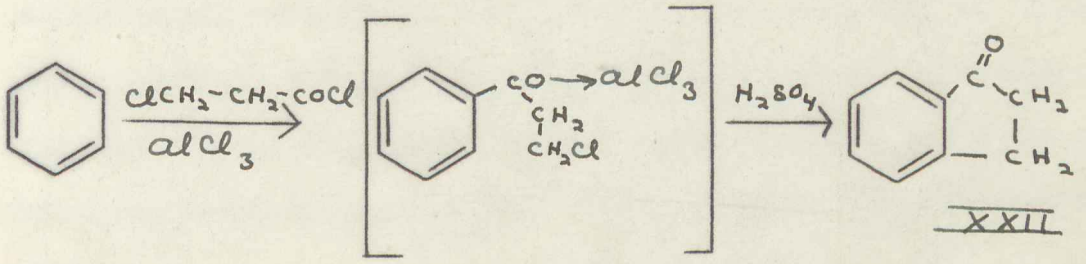


After standing overnight the mixture was extracted with 70 ml. of 2N hydrochloric acid and twice with 30 ml. of 5N hydrochloric acid. This aqueous solution was made neutral with ammonium hydroxide and then slightly acidic with hydrochloric acid. No crystallization resulted when the following solution was immersed in an ice water bath. This mixture was now heated gently to evaporate some of the liquid. At regular intervals the solution was cooled in the ice water bath but no crystals formed. The mixture was evaporated down to the point where ammonium chloride precipitated out when the solution was cooled.

Since the desired compound is amphoteric, the benzene

layer was now extracted with 10% sodium carbonate. Neutralization and cooling of the carbonate extract did not yield any product. The benzene solution was evaporated at an aspirator and the un-rearranged N-nitroso compound was collected.

19. Preparation of Indanone-1



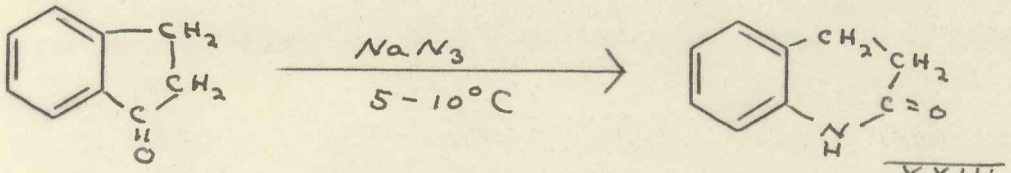
XXII

The preparation of indanone-1(XXII) was carried out under the same conditions as in the preparation of 4,7-dimethylindanone-1. The only difference is that benzene, instead of p-xylene, is the reacting aromatic nucleus. The reactants consisted of 0.21 moles of β-chloropropionyl chloride, 0.20 moles of benzene, and 0.24 moles of aluminum chloride. A yield of 43%(11g.) of indanone-1 melting at 38-39.5°C was obtained. Purification of the product was effected by vacuum distillation. Indanone-1 boils at 123-125°C at 15 mm. and yields a pale yellow solid.

20. Preparation of 3,4-Dihydrocarbostyril

The preparation of 3,4-dihydrocarbostyril(XXIII) was carried out by the method of Conley[15] and under the same

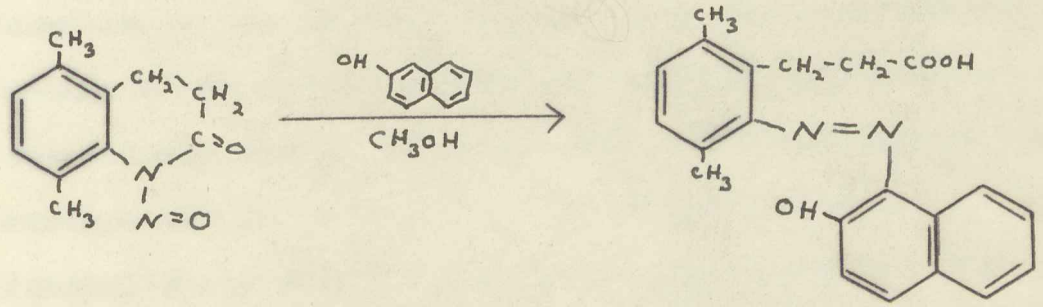
reaction conditions as used in the previous preparation of



XXIII

5,8-dimethylhydrocarbostyril(XVII). A yield of 55%(3.1g.) of the product melting at 162-163°C was obtained by using 0.04 moles of indanone-1 and 0.05 moles of sodium azide as the starting materials. Recrystallization of the 3,4-dihydrocarbostyril was carried out in a water-ethanol solvent system.

21. Attempted Coupling with β-Naphthol



An attempt was made to couple the 5,8-dimethyl-N-nitrosohydrocarbostyril with β-naphthol according to the method of Huisgen.(2) The N-nitroso compound(0.4g.) and β-naphthol(0.35g.) were dissolved in methanol(10.0 ml.). This mixture was heated for about 12 hours at 40°C and although the color of the solution did slightly change, there did not appear to be any distinct coupling. On gently refluxing this solution there appeared in the mixture a deep

red color characteristic of azo coupling. However no azo dye separated out on cooling this mixture and no product was isolated form the reaction. A spectrum of this reaction mixture was taken in the visible region and it is shown in Figure 6.

22. Attempted Reaarngement of 5,8-Dimethyl-N-Nitrosohydrocarbostyril with Base

An attempt was made to force the rearrangement of this N-nitrosolactam to go by an alternate mechanism, i.e., to cause rearrangement to proceed through an ionic rather than a free-radical mechanism. If, in actuality, the rearrangement of the compound proceeds through the trans-diazo ester, an ionic mechanism with base would aid in breaking the C-N bond and in the process it would free the compound from having to go through the highly strained eight-membered trans-diazo ester. Therefore this should facilitate the rearrangement procedure. Piperidine(0.002 moles) and the 5,8-dimethyl-N-nitrosohydrocarbostyril(0.002 moles) were mixed into 15 ml. of benzene and this mixture was allowed to stand for twelve days at room temperature. Extraction of the reaction mixture was carried out twice using 5 ml. of 10% sodium carbonate solution. The aqueous extract was made neutral with 6N hydrochloric acid and cooled in an ice water bath but no indazole product was able to be isolated.

23. Nitrogen Analysis

The 5,8-dimethyl-N-nitrosohydrocarbostyril was sent to the Microanalysis Company, Wilmington, Delaware for an analysis of its nitrogen content. The first nitrogen analysis was carried out on the crude product(without recrystallization) and a rather low nitrogen value was found as is seen below.

	Calc.	Found(1)	Found(2)
5,8-Dimethyl-N-Nitroso-hydrocarbostyril	13.70	12.81	13.25

Recrystallizing the N-nitroso compound twice from a methanol-water solvent system yielded a sample whose nitrogen content was substantially increased. The 5,8-dimethylhydrocarbostyril from which the N-nitrosolactam was prepared has a nitrogen content of 8.00 and therefore a small amount of this impurity will significantly alter the results obtained for the nitrogen analysis. A further discussion of this nitroso compound will be included in the summary where references will be made to spectral data.

DISCUSSION AND SUMMARY

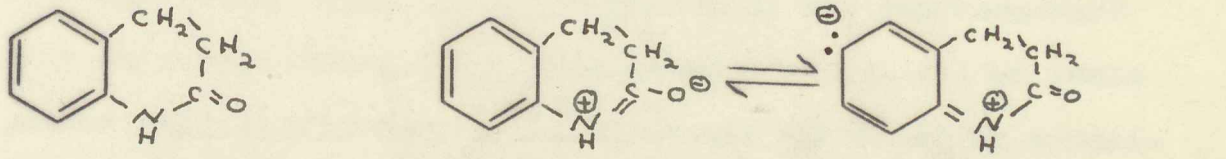
The rearrangement of the 5,8-dimethyl-N-nitrosohydrocarbostyril to 6-methyl-7-(β-carboxyacetyl)-indazole was unsuccessful. But before further discussion of the rearrangement, it is necessary to establish the existence of this stable N-nitrosolactam.

The most valuable information on its existence comes from the n.m.r. spectrum which contains bands at 2.30(3 protons of C_5;s), 2.70(3 protons of C_8;s), 2.90(2 protons of C_3;t), 3.90(2 protons of C_4;t), 7.20(1 proton of C_6;d), and 7.30 (1 proton of C_7;d). An infrared spectrum was run on this compound but it was of little consequence in identifying the product. Data on the absorption of the -N-N=O linkage could not be found in the literature because of the general instability of this type of bonding. A visible region spectrum was taken of the compound and it appears in Figure 1.

The presence of the N-nitrosolactam can be inferred from the nitrogen analysis since the existence of some different nitrogen-containing compound would have radically altered the nitrogen content of the sample. The n.m.r. spectrum rules out the possibility of a ring-substituted nitroso compound(-C-N=O) because of the bands at 7.20 and 7.30 which show the splitting between the two aromatic ring protons. Therefore the deviation between the calculated and found values of the nitrogen content is due to the impurity, 5,8-dimethylhydrocarbostyril, which was not completely removed by

recrystallization.

A rationalization as to why the N-nitroso product was obtained when two methyl groups were present on the aromatic ring is that these two methyl groups caused steric inhibition of the benzolactam resonance thus making nitrosation of the amide nitrogen more feasible.



Benzolactam Amide Resonance Aniline Resonance

Evidence for the thermal stability of the 5,8-dimethyl-N-nitrosohydrocarbostyril can be drawn from the fact that it melts at 81-82 C and does not undergo rearrangement in benzene even under vigorous refluxing conditions. It is seen that unfavorable steric factors will be encountered if the rearrangement must proceed through the trans-diazo ester as postulated by Huisgen. Furthermore the presence of the methyl group on C_8 will add to this unfavorable rearrangement condition. As was shown earlier, for the rearrangement to occur most rapidly a large membered ring(9 or more) is needed to free the system of strain. Furthermore as the N to N double bond becomes more coplanar with the aromatic ring, the rate and facility of rearrangement will be enhanced. In both cases the 5,8-dimethyl-N-nitrosohydrocarbostyril fails to meet these qualifications.

Figures 2 through 5 show various stages in the coupling

reaction of the N-nitroso compound with β-naphthol. While the mixture was refluxing, samples were removed at various intervals and they were analyzed in the visible region of the spectrum. From these spectra there is evidence that a change in the N-nitrosolactam is occurring but whether or not this indicates azo coupling has not been determined.

For future work it is foreseen that the rearrangement must be forced through a different mechanism,i.e., an ionic rather than a free-radical route as was discussed in experiment 22. For this purpose it is suggested to continue the investigation using base(piperidine) for the rearrangement to indazole and for the coupling with -naphthol, and if more vigorous conditions are deemed necessary, potassium hydroxide or alcoholic sodium methoxide should be used. Investigation into the possibility of nitrosating 3,4-dihydrocarbostyril could be continued and spectral studies on the existent N-nitrosolactam could be expanded but presently this seems to be of minor importance.

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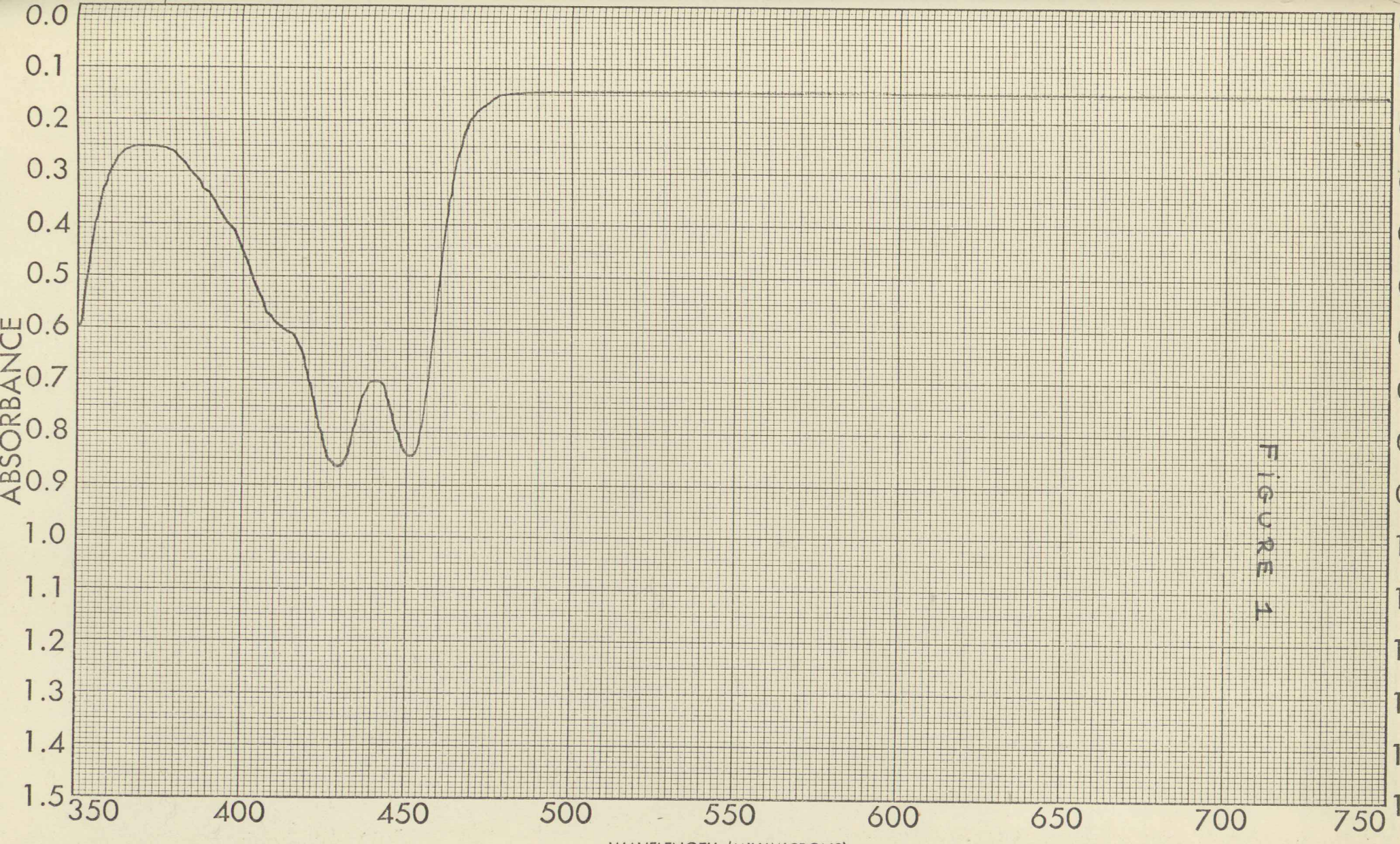
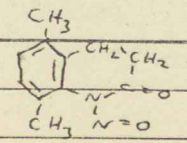


Figure 1

SAMPLE 	CURVE NO.	SCAN SPEED Slow	OPERATOR R. A. D.
	CONC.	SLIT 40	DATE 4/22/66
ORIGIN	CELL PATH	REMARKS	
SOLVENT CH_3OH	REFERENCE CH_3OH		

PART NO. 202-1512

PERKIN-ELMER

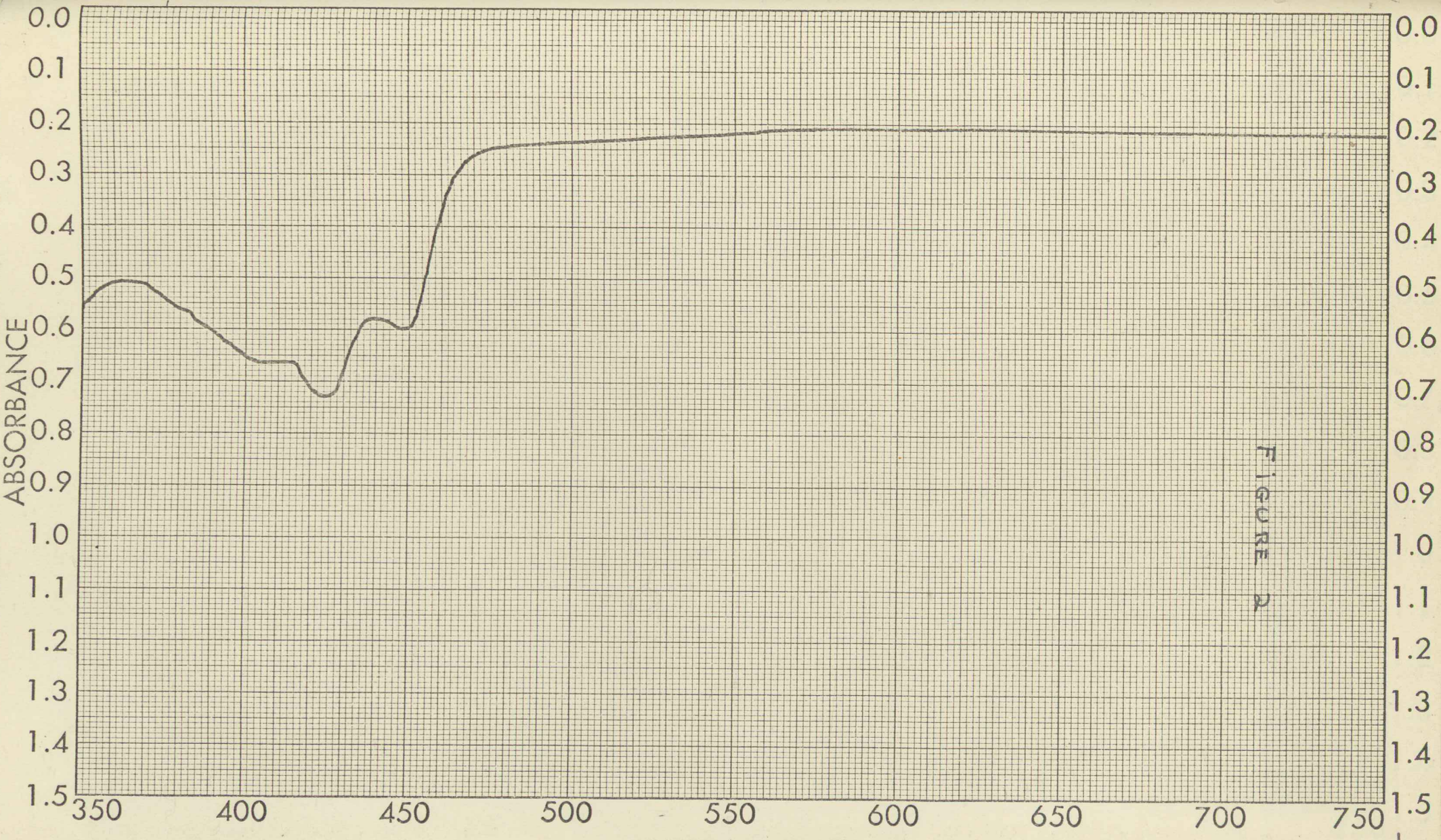
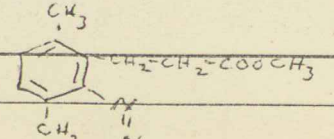
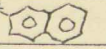


Figure 2



SAMPLE	CURVE NO. I	SCAN SPEED Slow	OPERATOR R. A. D.
	CONC.	SLIT 40	DATE 4/22/66
ORIGIN	CELL PATH	REMARKS	
SOLVENT CH_3OH	REFERENCE CH_3OH + 		

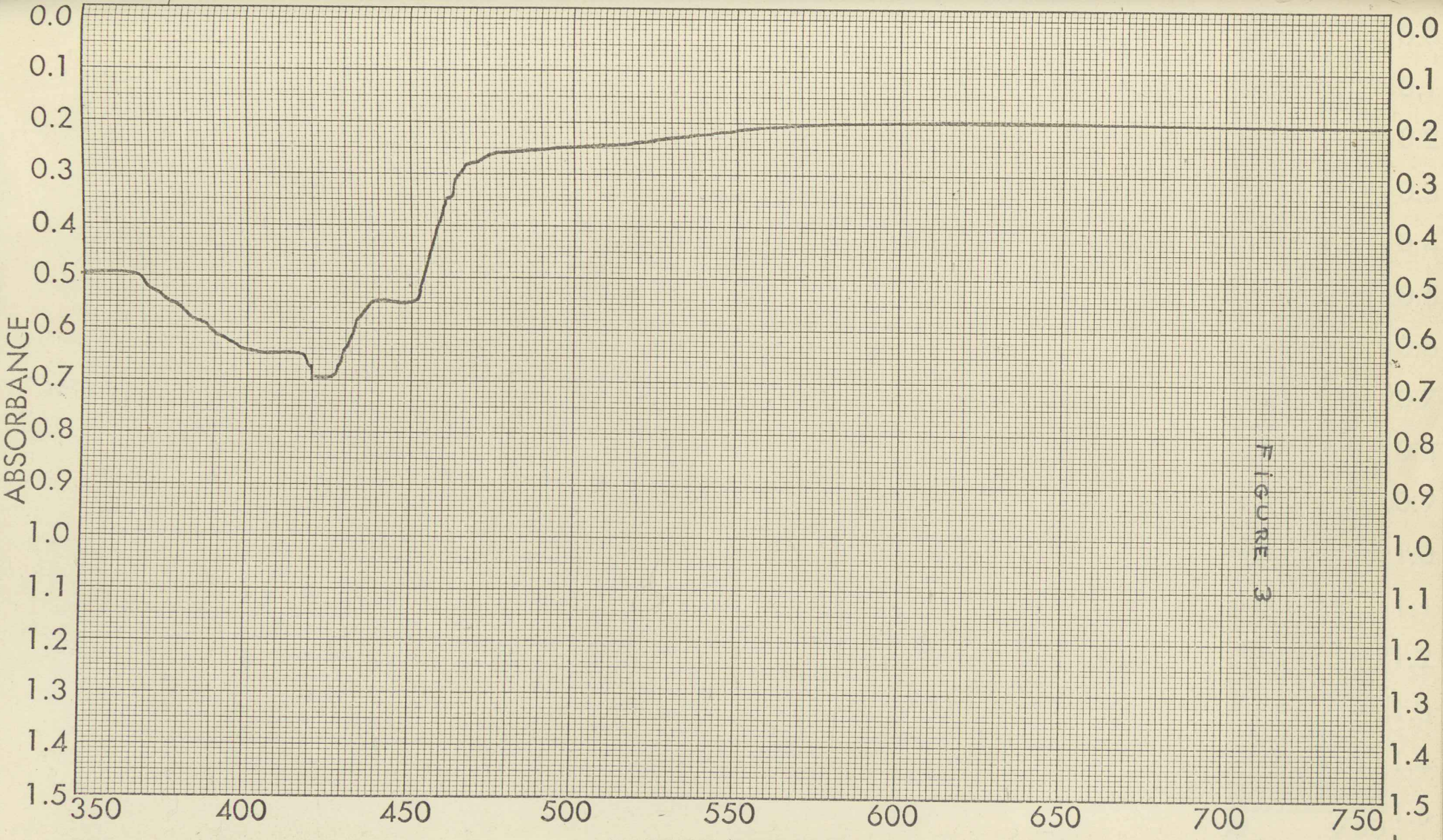
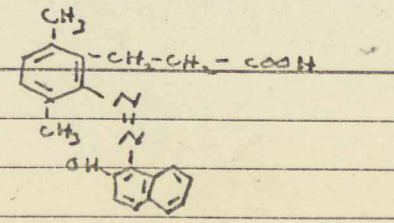


FIGURE 3



SAMPLE

ORIGIN

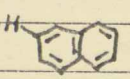
SOLVENT CH_3OH

CURVE NO. II

CONC.

CELL PATH

REFERENCE CH_3OH +



SCAN SPEED Slow

SLIT 40

OPERATOR R. A. D.

DATE 4/27/66

REMARKS

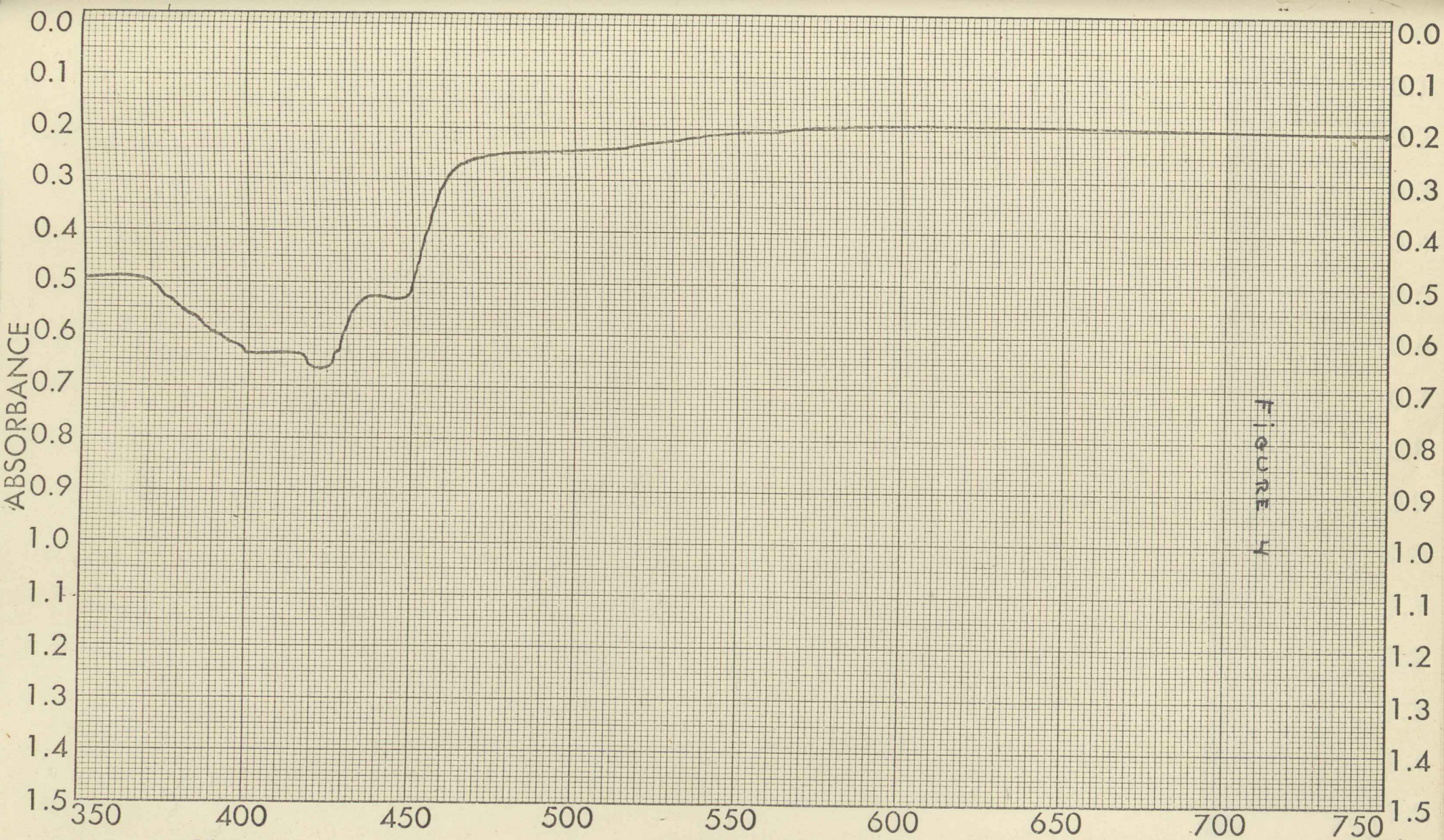
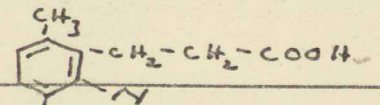
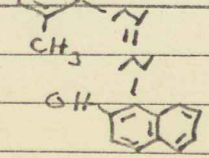


Figure 4

-33-



SAMPLE 	CURVE NO. III	SCAN SPEED Slow	OPERATOR R. A. D.
	CONC.	SLIT 40	DATE 4/27/66
ORIGIN	CELL PATH		REMARKS
SOLVENT CH_3OH	REFERENCE CH_3OH + 		

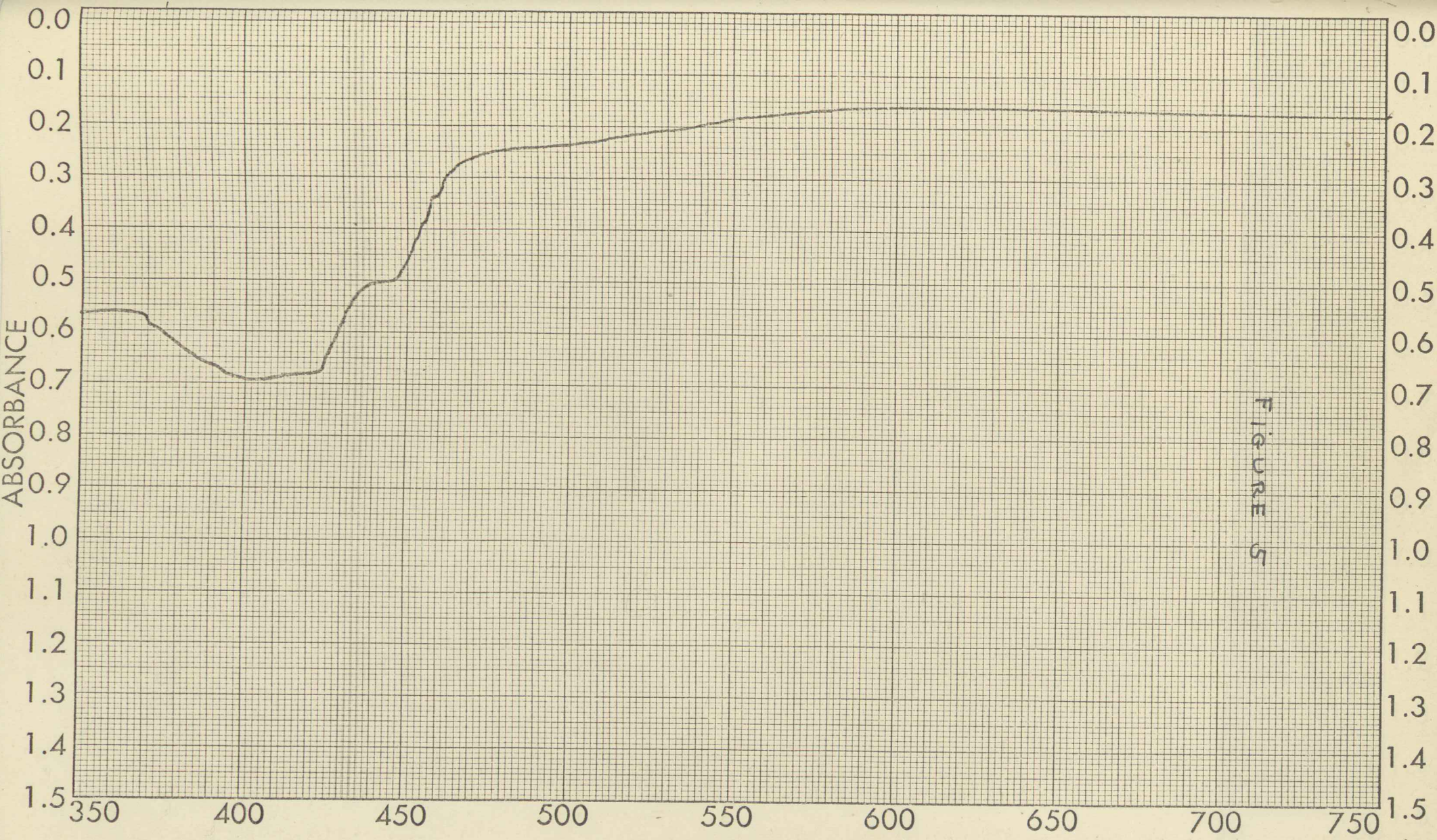
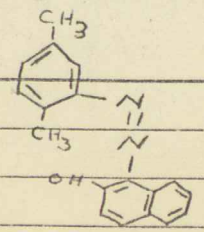
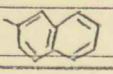


FIGURE 5



SAMPLE	CURVE NO. IV	SCAN SPEED Slow	OPERATOR R.A.D.
	CONC.	SLIT 40	DATE 4/28/66
ORIGIN	CELL PATH	REMARKS	
SOLVENT CH_3OH	REFERENCE CH_3OH + 		

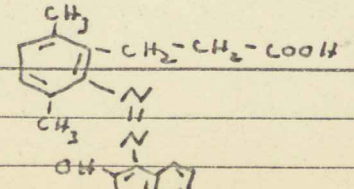
ABSORBANCE

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5

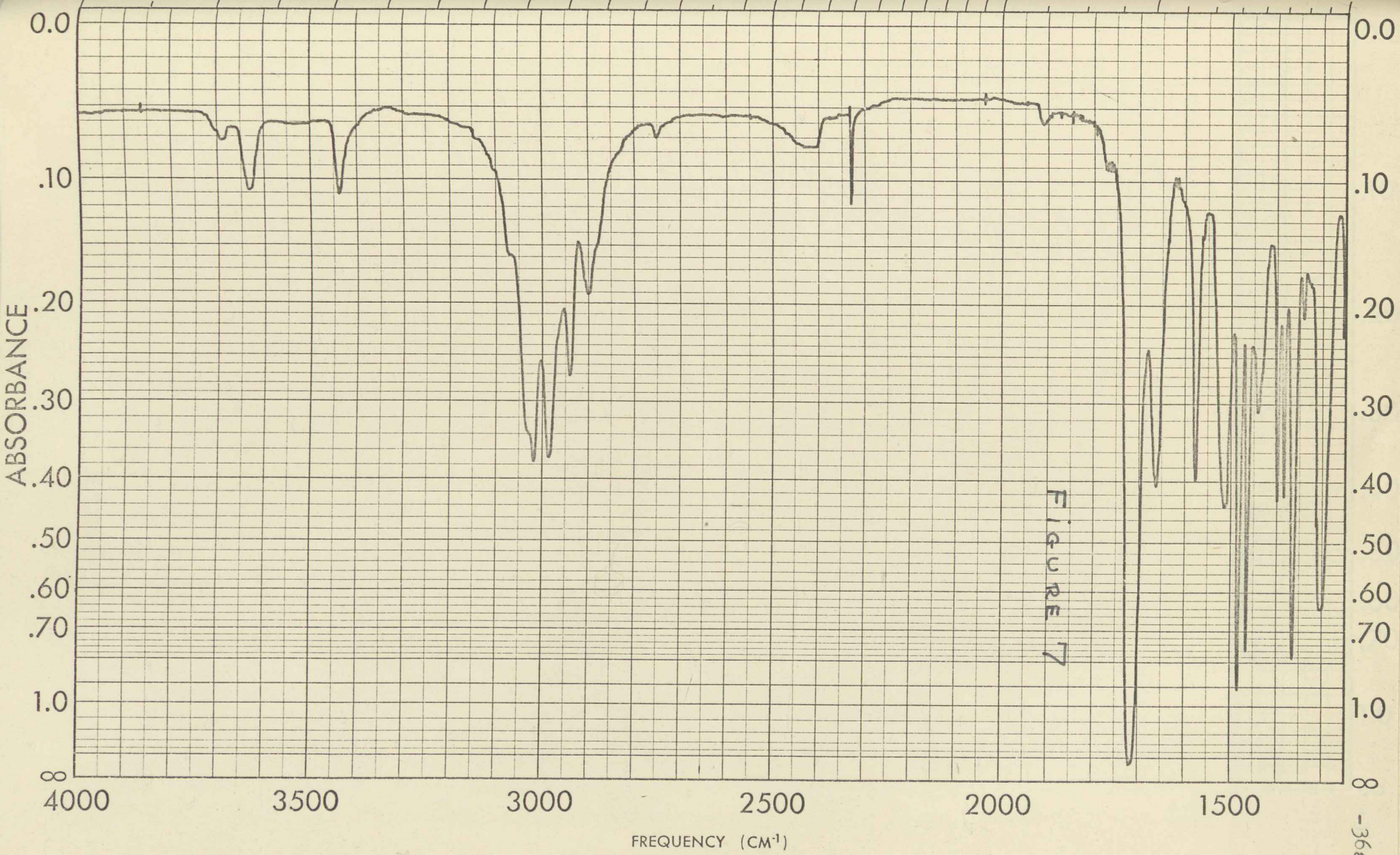
350 400 450 500 550 600 650 700 750

WAVELENGTH (MILLIMICRONS)

FIGURE 6

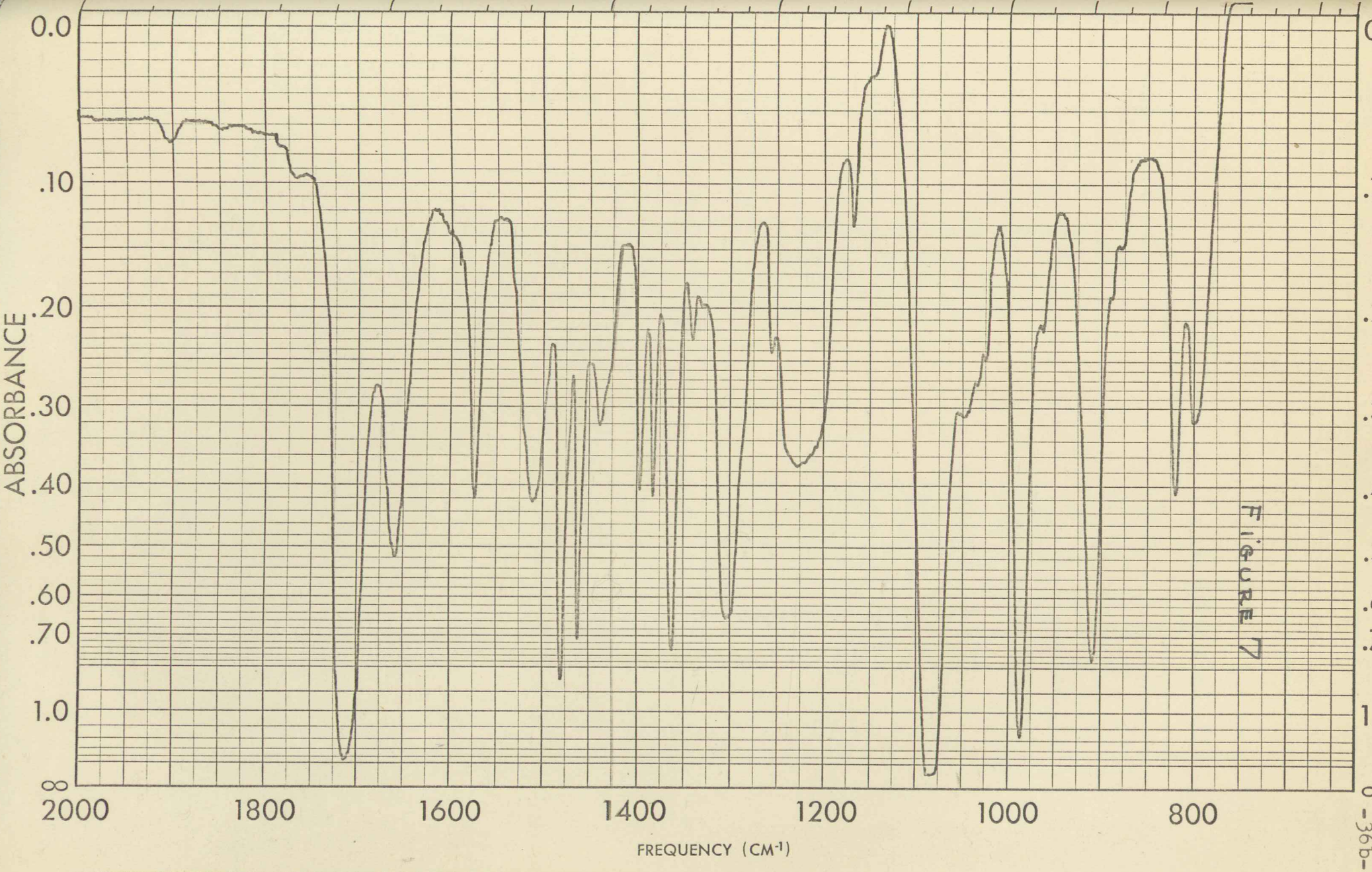


SAMPLE	CURVE NO.	SCAN SPEED Slow	OPERATOR R.A.D.
	CONC.	SLIT 40	DATE 12/13/65
ORIGIN	CELL PATH	REMARKS	
SOLVENT Methanol	REFERENCE Methanol + β-Naphthol		



SAMPLE 5,8 - Dimethyl - N - Nitrosohydrocarbostyril	CURVE NO.	SCAN SPEED	OPERATOR R. A. D.
ORIGIN	CONC. 5%	SLIT	DATE 4/27/66
SOLVENT Chloroform	CELL PATH	REMARKS	
	REFERENCE Chloroform		

PERKIN-ELMER



SAMPLE 5,8-Dimethyl-N-Nitrosohydrocarbostyril	CURVE NO.	SCAN SPEED	OPERATOR R. A. D.
ORIGIN	CONC. 5%	SLIT	DATE 4/27/66
SOLVENT Chloroform	CELL PATH	REMARKS	
	REFERENCE Chloroform		

PERKIN-ELMER

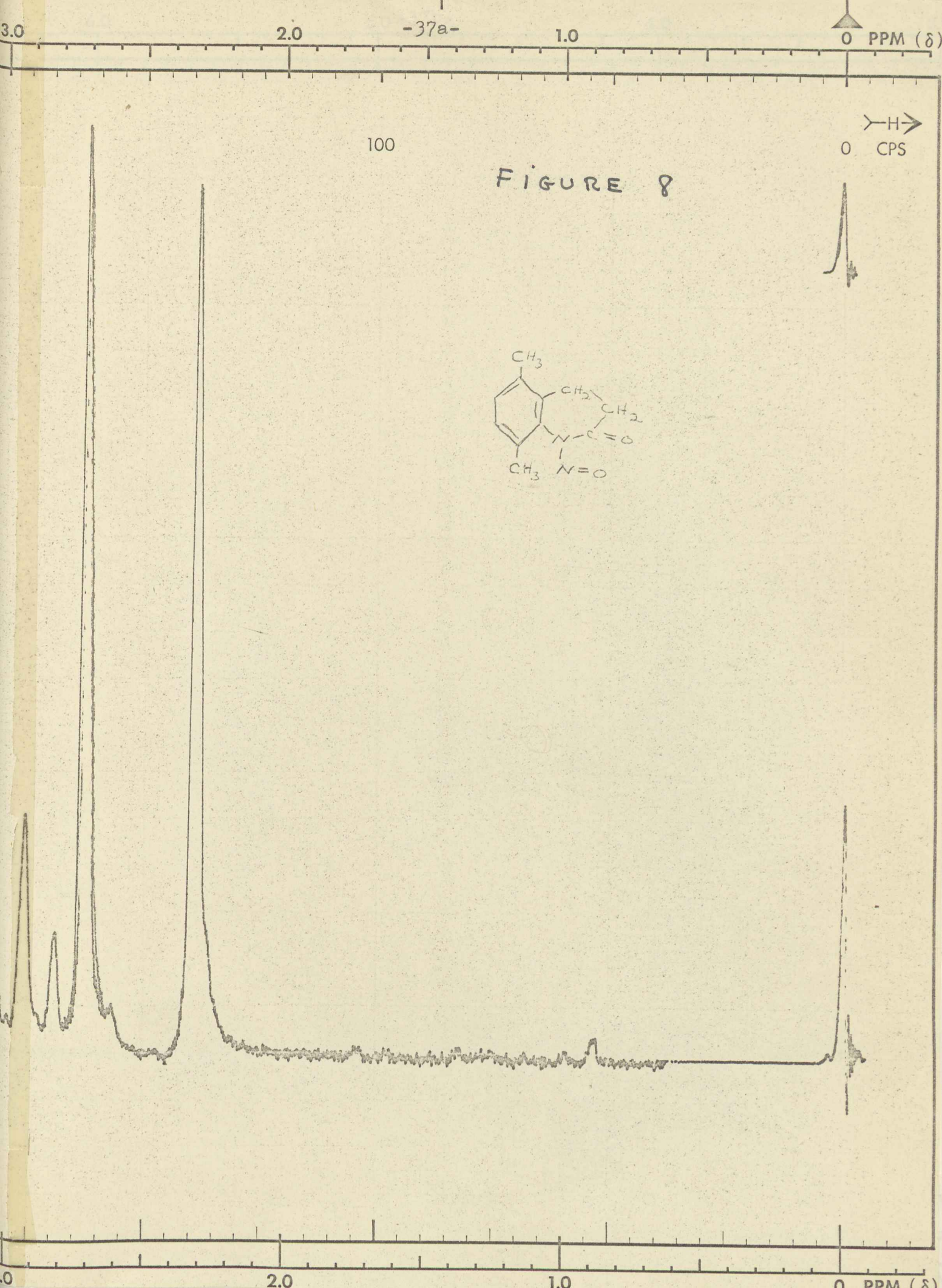
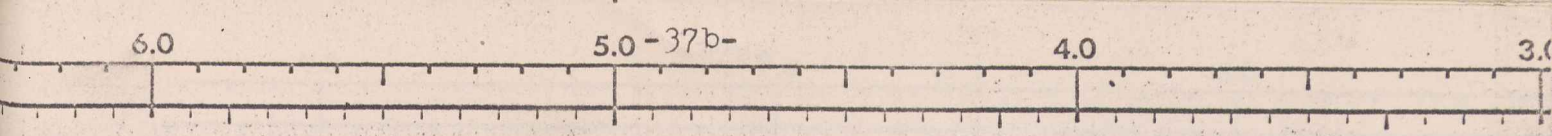
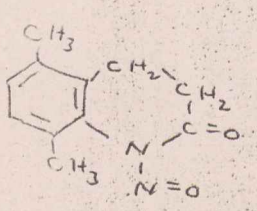


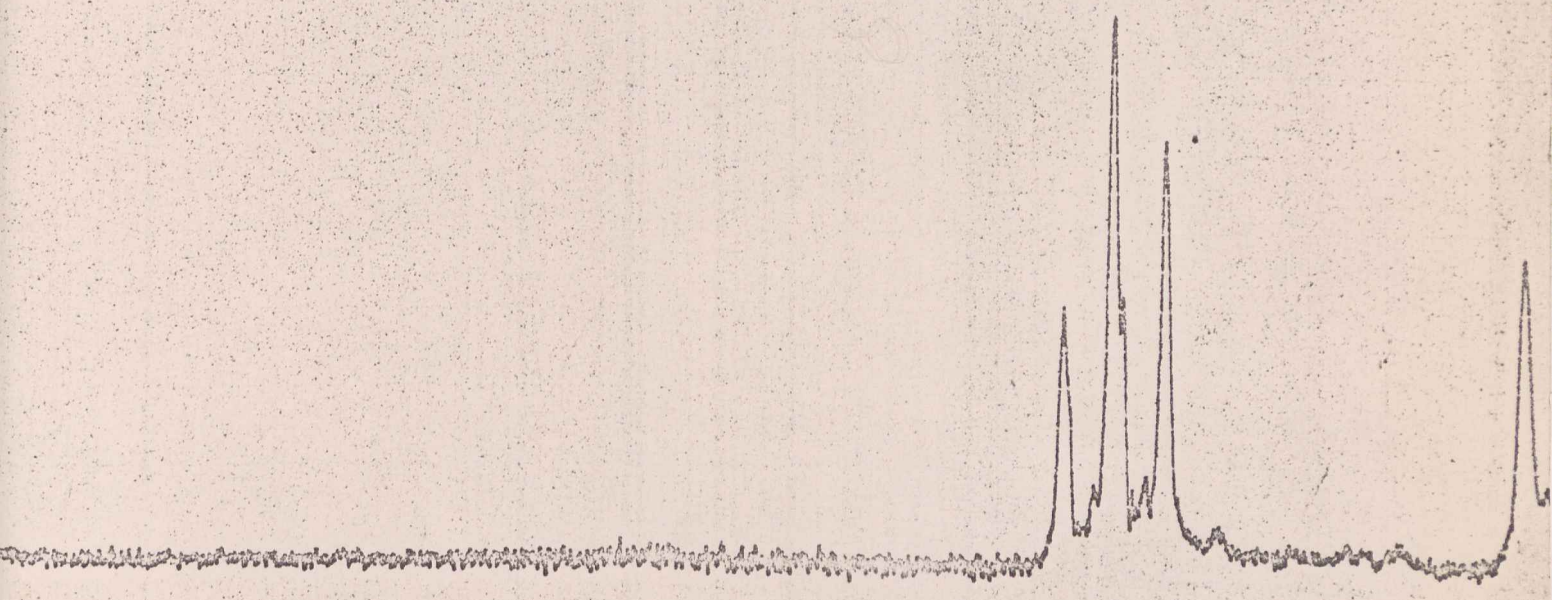
FIGURE 8

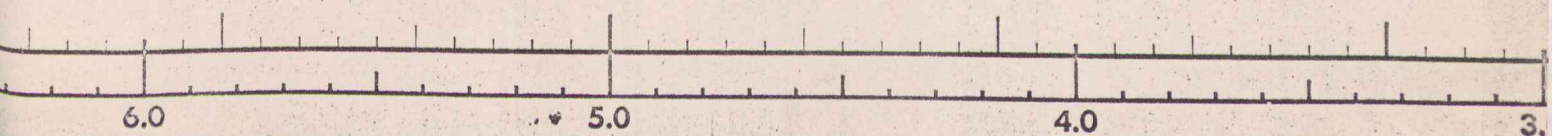


300 200

FIGURE 8







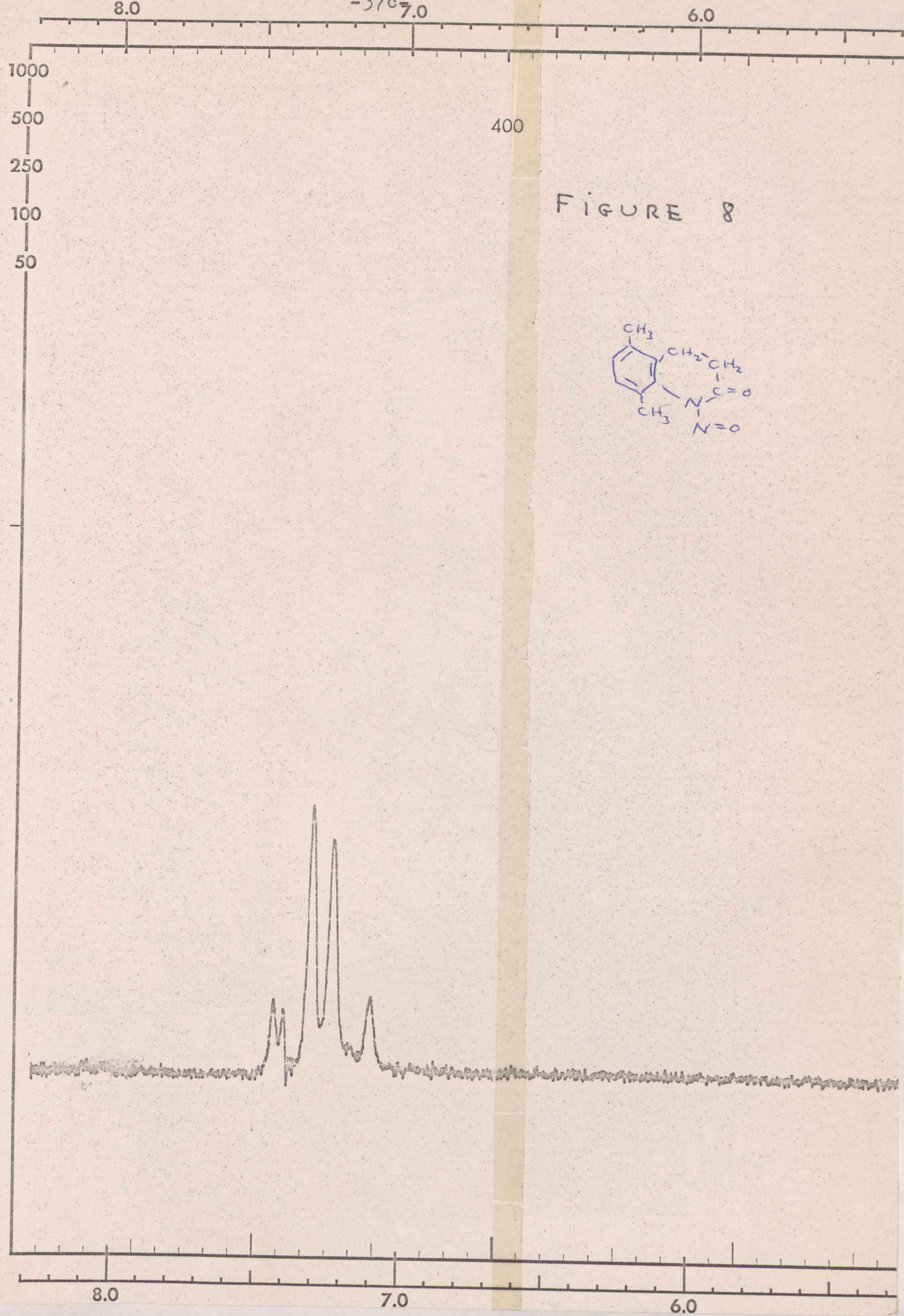


FIGURE 8

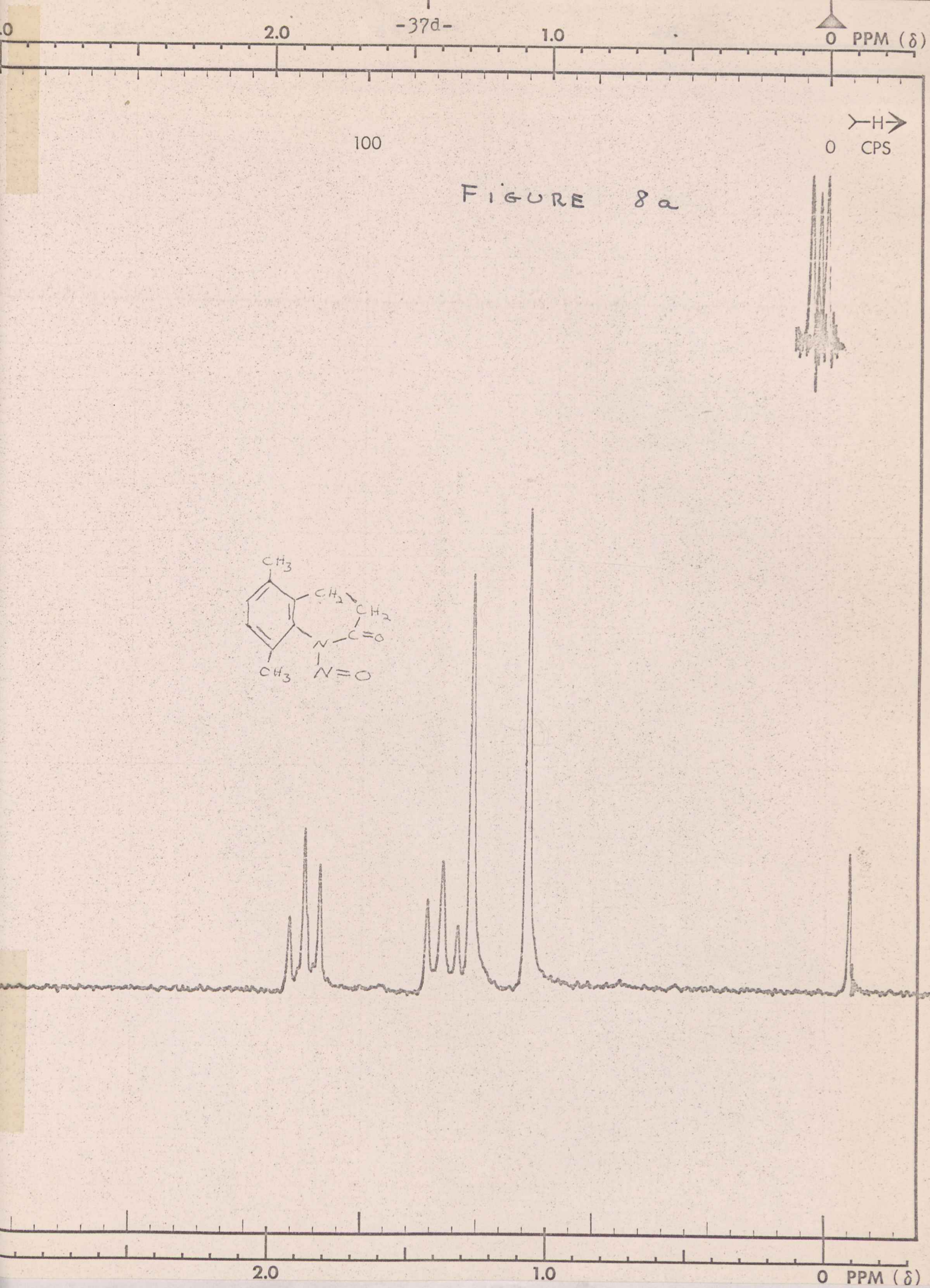
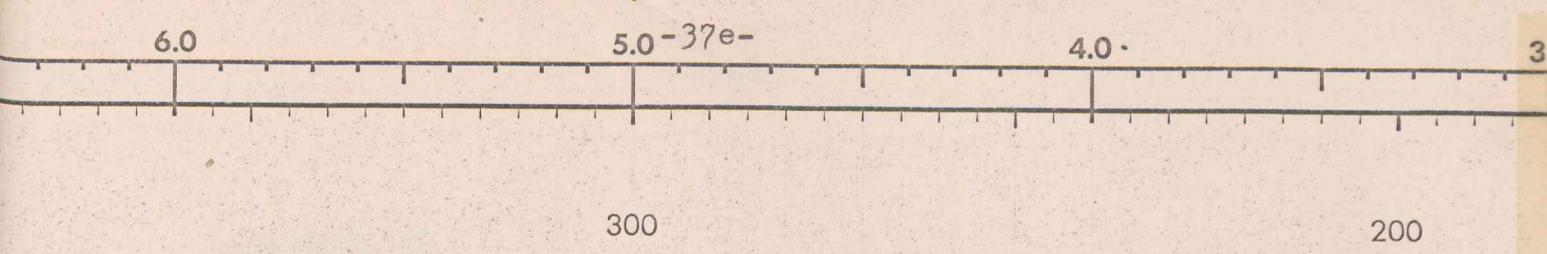
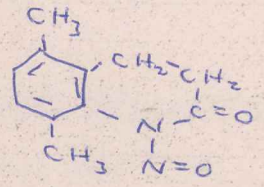


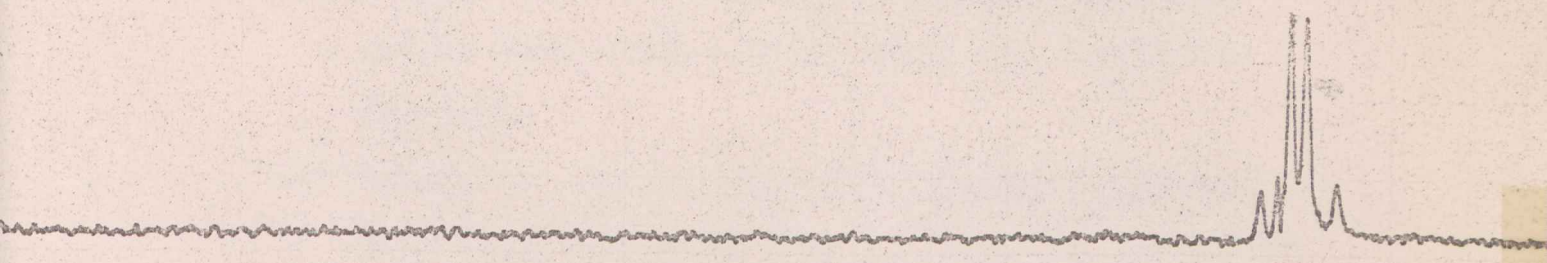
FIGURE 8a

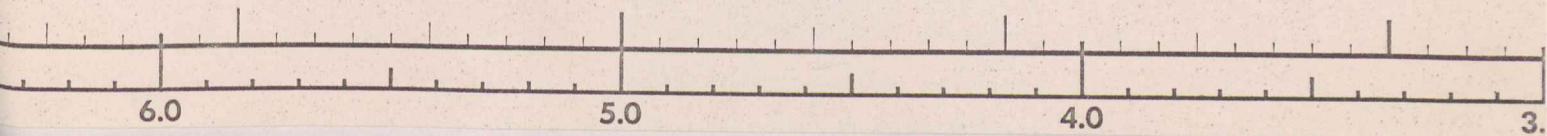


300 200

FIGURE 8a







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